REMARKS

Claims 1-13 were examined in the February 8, 2008 Office Action. The election without traverse in response to a Second Restriction Requirement of claims 1-12 (Group II) is acknowledged. The election of species is acknowledged, with the result that claims 1 and 2 are examined herein. However, claim 1 is believed to be generic, and if prosecution of the species of claim 2 leads to an indication of allowable subject matter, applicant reserves the right to request reopening of prosecution for the species of one or more of claims 3-12.

To obtain full benefit of foreign priority, a copy of a certified English translation of the Austrian priority application is submitted herewith. With regard to the drawings, Figs. 7 and 8 stand objected to as too dark and lacking detail. The specification is objected to as lacking headings. Claims 1 and 2 are rejected under 35 U.S.C. 101, because the claimed use does not contain any process steps. Claims 1 and 2 are further rejected as anticipated by *Virgolini* ("Beneficial effect of long-term PGE_1-treatment in left ventricular heart failure").

Reconsideration of the objections and rejections is requested in view of the above amendments and the remarks which follow.

A. Priority and Submittal of Certified Translation.

Enclosed herewith is a certified translation of priority Austrian Application No. 1635/99. Full priority benefit is respectfully requested.

B. Objection to the Drawings is Addressed.

Replacement drawings are enclosed herewith in which the detail lacking in the previous copies now appears. Withdrawal of the objection is requested.

C. Objection to the Specification is Addressed.

The disclosure is objected to as not including the following section heading: "Brief Description of the Drawings." The amendments above to the specification add all required headings. Withdrawal of the objection is respectfully requested.

D. §112, 2nd Paragraph Rejection of Claims 1-2 is Addressed.

The indefiniteness rejection of claims 1-2 is respectfully traversed. Claims 1 and 2 have been amended to positively recite method steps of the claimed

process. Support for these amendments is found, for example, at page 6, line 36 – page 12, line 9 of the specification. No new matter is added thereby. In view of the above amendments, withdrawal of the § 112, 2nd paragraph rejection of claims 1-2 is respectfully requested.

E. §101 Rejection of Claims 1-2 is Addressed.

The issues relating to absence of claimed process steps has been addressed by the amendments to claims 1 and 2 discussed above. In view of the above amendments, withdrawal of the § 101 rejection of claims 1-2 is respectfully requested.

F. Anticipation Rejection of Claims 1 and 2 by *Virgolini* is Addressed.

The rejection of claims 1 and 2 under 35 U.S.C. § 102(b) over *Virgolini* is respectfully traversed.

Claim 1, as amended, is directed to a method of inducing angioneogenesis in a subject. The method comprises administering to a subject a medicament containing alprostadil such that angioneogenesis is induced in the subject. As shown on pages 8 to 11 of the specification, the HTX followed by immunohistochemical investigation and comparison of the capillary density of the explanted hearts of patients with preceding alprostadil infusion therapy and patients without alprostadil therapy were conducted to prove that an aldoprostadil infusion therapy may be undertaken for the purpose of neovascularization. Evidence supporting the claimed methodology of using alprostadil for neovascularization in the hearts of patients with cardiomyopathy is found at page 11, lines 16 to 20 of the specification.

Virgolini describes treating patients with congestive heart failure with PGE1 at 10-30 ng/kg/min. As a result, the left ventricular ejection fraction (LVEF) was improved. The therapeutic benefit observed is asserted by *Virgolini* to be mediated by a combined action of PGE1 on myocardial contractility and afterload reduction. *See Virgolini* (copy attached as Exhibit A), page 179, right column, 1st full paragraph. Although *Viroglini* teaches the treatment of congestive heart failure/congestive cardiomyopathy with alprostadil, the treatment taught by *Virgolini* is based on vasodilating effects which result from peripheral injection, and *Virgolini* neither teaches nor suggests the angioneogenesis enhanced by alprostadil. Indeed, *Virgolini* uses left ventricular ejection fraction (LVEF) to

evaluate the treating effect of alprostadil (*see*, page 178, left column) and suggests that the therapeutic benefits observed, improving life-quality and extending the time for transplant availability, may be mediated by a combined action of PGE1 on myocardial contractility and after load reduction, although no significant alteration in blood pressure and heart rate occurred (*see* page 179, left column, second paragraph). Ventricular ejection, myocardial contractility and after load reduction are known parameters in the art to determine vasodilating effects (*see* Exhibit B "Critical Care Medicine, 1994, Vol. 22, No. 7, pp. 1084-1090"). Another reference, "Journal of Heart and Lung Transplantation, May 1997, pp. 556-61 (*see* Exhibit C hereto) also concludes that PGE are potent endogenous vasodilators that also have the activity of sympathetic nervous system and will increase ventricular ejection and increase myocardium contractility also pre-load and after-load reduction (*see* page 557, right column, first paragraph and page 560, left column, third paragraph). These references make it clear that the only observed changes noted relate to the ventricular ejection fraction and after load reduction which are seen as relevant to vasodilatation.

Because *Virgolini* fails to teach or suggest the claimed method of administering PGE1 to a subject to induce angioneogenesis, *Virgolini* cannot anticipate claim 1. By the same token, claim 2, dependent from claim 1, is also novel over *Virgolini*. Withdrawal of the anticipation rejection of claims 1 and 2 is thus proper and respectfully requested.

G. New Claims 14 and 15

New claims 14 and 15, dependent from claims 1 and 2, respectively, are added. In the methods of claims 14 and 15, the medicament is administered to the subject via a central right-heart catheter with an initial dose of 2.5 ng/kg/min, which is then increased to the maximally tolerated dose (MTD) of 29 ± 1 ng/kg/min. Support for claims 14 and 15 can be found, for example, at page 8, lines 9-20 of the specification. No new matter is introduced.

Claims 14 and 15 are novel over *Virgolini* for at least the same reasons provided above with respect to claim 1. Further, PGE1 is administered via different methodologies at different dosage levels in *Virgolini* and the present invention. More specifically, in *Virgolini*, patients received cyclodextrin-PGE1 at

increasing dose rates (10-100 ng/kg/min, i.v.) using a Precidor pump for 10 minutes each. 20 ng PGE1/kg/min was then administered i.v. using a portable pump and a peripheral venous access on a long-term basis. (See, e.g., the paragraph bridging pages 177 and 178.) In the present invention, the PGE1 infusion took place via a central right-heart catheter with an initial dose of 2.5 ng/kg/min, which was then increased to the MTD of 29 $\pm$ 1 ng/kg/min. The MTD was halved in the following 12 hours, and the therapy was continued with a portable pump at home. (*See*, page 8, lines 9-20 of the specification.) As a result, the LVEF was improved due to pulmonary vasodilation or enhanced myocardial contractility by PGE1 in *Virgolini*, while angioneogenesis is induced by PGE1 in the present invention. Therefore, claims 14 and 15 are not anticipated by *Virgolini*.

H. Conclusion.

Pending claims 1, 2 and 14-15 are now believed to be in form for allowance and such action is respectfully requested. Should any issues remain, the Examiner is kindly asked to telephone the undersigned.

I. Petition for 3-Month Extension and Applicability of Small Entity Status.

The undersigned hereby petitions for a 3-month extension in which to respond to the Office Action and also notifies the U.S. Patent & Trademark Office that Small Entity Status applies to the present application. Please charge Deposit Account No. 50-1123 the small entity 3-month extension fee and any other fees deemed associated with this filing.

Respectfully submitted,

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